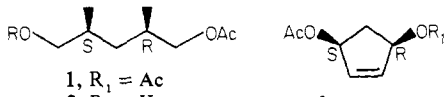
prediction of the enantiomeric excess (ee) of the monoester fraction and the optimization of optical and chemical yields.

To confirm the validity of our theoretical considerations, we selected two meso esters, 1,5-diacetoxy-*cis*-2,4-dimethylpentane[7a] (**1**) and *cis*-3,5-diacetoxycyclopent-1-ene[7b] (**3**), as model substrates for incubation with two different enzymes, pig pancreatic lipase (PPL) and pig liver esterase (PLE).[3]



1, R_1 = Ac
2, R_1 = H

3, R_1 = Ac
4, R_1 = H

A solution of **1** (1.08 g) in 0.1 M phosphate buffer, pH 7.0 (150 mL), was incubated with PPL (200000 units, Sigma Type VI S) at 25 °C with stirring. At various intervals, the extent of conversion and the ee of the monoacetate fraction were determined.[6] A sample of the monoacetate, **2**, $[\alpha]^{25}_D$ −9.5° (89.7% ee), was transformed into the known (2*S*,4*R*)-2,4-dimethylvalerolactone, $[\alpha]^{25}_D$ +36.9° [lit.[1a] (2*R*,4*S*) −41.1°], indicating that the *pro-S* acetoxy group of **1** was preferentially cleaved by PPL. When eq 1 and 2 were used, the kinetic constants for the hydrolysis of **1** were calculated to be $\alpha = 15.6 \pm 0.5$, $E_1 = 0.036 \pm 0.002$, and $E_2 = 0.18 \pm 0.01$. As can be seen from Figure 1, the experimental data are in good agreement with the computer-generated curves for these kinetic constants. On the other hand, PLE preferentially hydrolyzed the *pro-R* acetoxy group of **1** and afforded kinetic constants of $\alpha = 2.47 \pm 0.36$, $E_1 = 0.22 \pm 0.05$, and $E_2 = 0.60 \pm 0.10$ (ee = 0.80, 36% yield; ee = 0.95, 15% yield).

In a similar experiment, **3** (920 mg) was exposed to PLE (1500 units) in 150 mL of 0.1 M phosphate buffer, pH 7.0. The resulting monoacetate, **4**, $[\alpha]^{25}_D$ −56.3° (80.3% ee), was established[8] to be 3(*S*)-acetoxy-5(*R*)-hydroxycyclopent-1-ene, confirming that the *pro-R* acetoxy group of **3** was preferentially attacked by PLE. The kinetic constants for the hydrolysis of **3** were $\alpha = 8.44 \pm 0.56$, $E_1 = 0.06 \pm 0.01$, and $E_2 = 0.12 \pm 0.02$.[9] On the basis of the computer-generated graph (not shown), the maximal recovery obtainable of the monoacetate fraction was 83% with an ee of 81%. Recrystallization of the monoacetate fraction (ee = 81.5%) from benzene–Skelly B (1:5) afforded **4** (ee >96%).

The essential feature of this approach lies in the recognition of the importance of the inherent consecutive kinetic resolution step in enhancing the optical purity of the chiral species during enantioselective hydrolysis of diesters. It is noteworthy that even though the α-value for the initial enantioselective hydrolysis step may be low, high optical purity of the desired chiral intermediate may still be obtained in fair yield. In principle, this concept is of general applicability to biochemical processes involving enantiotopic group differentiation. Consequently, this strategy provides synthetic chemists with considerably more flexibility in the selection of enzyme systems for asymmetric syntheses.

Acknowledgment. We thank Professor J. Fried for a generous supply of *cis*-3,5-dihydroxycyclopent-1-ene. This investigation was supported in part by Grant HL 25772 of the National Institutes of Health.

Supplementary Material Available: Derivations of equations, determination of kinetic parameters, and description of analytical methods (4 pages). Ordering information is given on any current masthead page.

(7) (a) Compound **1** was prepared by LAH reduction of dimethyl *cis*-2,4-dimethylglutarate[1a] followed by acetylation (Ac_2O/Pyr). (b) Compound **3** was prepared by acetylation of *cis*-3,5-dihydroxycyclopent-1-ene, kindly provided by Professor Josef Fried.

(8) The monoacetate **4**, was transformed to the known (+)-3(*S*)-hydroxy-5(*R*)-(tetrahydropyranoxy)cyclopent-1-ene, $[\alpha]^{23}_D$ +17.8°. See: Nara, M.; Terashima, S.; Yamuda, S. *Tetrahedron* **1980**, *36*, 3161.

(9) Although conventional preparations of PLE were shown to be heterogenerous (Ferb, D.; Jencks, W. P. *Arch. Biochem. Biophys.* **1980**, *203*, 214), the experimental data were in accord with the predictions of eq 1 and 2.

Reactivities of Activated Metal Carbonyl Clusters. Ligand Substitution Kinetics of the Methoxycarbonyl Adduct $Ru_3(CO)_{11}(CO_2CH_3)^-$

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Investigations in this laboratory have been concerned with the activation of coordinated carbon monoxide by oxygen containing nucleophiles in context of the mechanistic details of the base-catalyzed water gas shift reaction.[1] In the course of these studies with trinuclear group 8 metal carbonyls, it was noted that reactions with methoxide to give methoxycarbonyl adducts $M-CO_2CH_3^-$ also activated the cluster to ligand substitution both by ligands in solution and by coordinated ligands capable of shifting from a monodentate to a bidentate coordination mode.[2] Reported here is a kinetics investigation showing the methoxycarbonyl adduct $Ru_3(CO)_{11}(CO_2CH_3)^-$ to be orders of magnitude more labile than the parent compound $Ru_3(CO)_{12}$. Such quantitative information is of considerable interest given that methoxycarbonyl adducts are proposed as intermediates in several catalytic cycles[3] and that ligand substitution is a key feature of homogeneous catalysis mechanisms.

When $NaOCH_3$ is added to a solution of $Ru_3(CO)_{12}$ under CO, a stable methoxycarbonyl adduct (A) is formed (eq 1), which can be isolated as the PPN^+ salt, $[PPN][Ru_3(CO)_{11}(CO_2CH_3)]$[4a] ($PPN^+$ = bis(triphenylphosphine)iminium).

$$Ru_3(CO)_{12} + OCH_3^- \rightleftharpoons \underset{A}{Ru_3(CO)_{11}(CO_2CH_3)^-} \quad (1)$$

Reactions of A with trimethyl phosphite in solution under CO results in the formation of the neutral products $Ru_3(CO)_{11}P(OCH_3)_3$ (eq 2) or $Ru_3(CO)_{10}(P(OCH_3)_3)_2$, depending upon the

$$Ru_3(CO)_{11}(CO_2CH_3)^- + P(OCH_3)_3 \rightarrow Ru_3(CO)_{11}(P(OCH_3)_3) + OCH_3^- + CO \quad (2)$$

conditions. In 10/90 THF/CH_3OH (v/v), addition of excess $P(OCH_3)_3$ gave $Ru_3(CO)_{11}P(OCH_3)_3$ (eq 2) as evidenced by infrared and electronic spectral changes. Stopped flow kinetics[4b] of this reaction showed that for $[P(OCH_3)_3] >> [Ru_3]$, plots of $\ln(Abs - Abs_\infty)$ vs. time were linear, indicating the rate law to be first order with respect to the cluster concentration. Plots of k_{obsd} vs. $[P(OCH_3)_3]$ were nonlinear, but k_{obsd}^{-1} vs. $[P(OCH_3)_3]^{-1}$ plots were linear with nonzero intercepts (Figure 1). Such plots at different CO pressures displayed different slopes but identical

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(4) (a) Elemental Analysis of $[PPN][Ru_3(CO)_{11}(CO_2CH_3)]$ calcd: Ru, 25.1; C, 48.67; H, 2.73; N, 1.16; P, 5.13. Found: Ru, 24.95; C, 48.56; H, 2.79; N, 1.18; P, 5.23. (b) $[Ru_3] = 2.6 \times 10^{-4}$ M, $[NaOCH_3] = 5.2 \times 10^{-3}$ M, THF and CH_3OH solvents were freshly distilled, freeze degassed, and then saturated with the appropriate gas. $[P(OCH_3)_3]$ ranged from 3×10^{-3} to 0.1 M.

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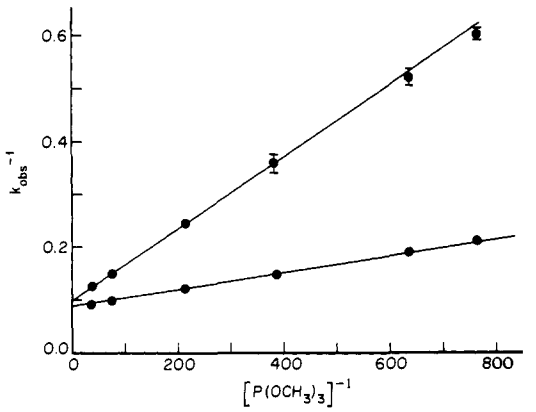

Figure 1. Double-reciprocal plots (k_{obsd}^{-1} vs. $[P(OCH_3)_3]^{-1}$) of the rate data for the reaction of $Ru_3(CO)_{11}(CO_2CH_3)^-$ with $P(OCH_3)_3$ in 90/10 CH_3OH/THF at 25 °C. Upper curve, P_{CO} = 1.0 atm; lower curve, P_{CO} = 0.25 atm.

intercepts (within experimental uncertainties, see Figure 1).

These observations are consistent with the following mechanism:

$$Ru_3(CO)_{11}(CO_2CH_3)^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{B}{Ru_3(CO)_{10}(CO_2CH_3)^-} + CO \quad (3)$$

$$Ru_3(CO)_{10}(CO_2CH_3)^- + L \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{C}{Ru_3(CO)_{10}L(CO_2CH_3)^-} \quad (4)$$

$$Ru_3(CO)_{10}L(CO_2CH_3)^- \overset{K_3}{\rightleftharpoons} Ru_3(CO)_{11}L + OCH_3^- \quad (5)$$

If k_{-2} is small and K_3 large,[5] then

$$k_{obsd} = k_1k_2[L]/(k_{-1}[CO] + k_2[L]) \quad (6)$$

and the plots in Figure 1 give k_1^{-1} for the intercept and $k_{-1}[CO]/(k_1k_2)$ for the slopes. The values of k_1 obtained thus (10.4 ± 1.1 s^{-1} at 25 °C) are independent of P_{CO} and gave the activation parameters $\Delta H^\ddagger$ = 12 ± 2 kcal/mol and $\Delta S^\ddagger$ = −13 ± 3 (cal/K)/mol. From the $k_2/k_{-1}[CO]$ value of 1.5×10^2 M^{-1} (25 °C, P_{CO} = 1.0 atm) and the estimated [CO] of ~0.008 M under these conditions,[7] a k_2/k_{-1} ratio near unity is estimated, indicating that the intermediate B is relatively unselective between the incoming ligands $P(OCH_3)_3$ or CO.[6]

In a 90/10 THF/CH_3OH solvent mixture, $Ru_3(CO)_{10}(P(OCH_3)_3)_2$ is the eventual product, however, sequential reactions to form the monosubstituted, then the disubstituted, products can be observed. The different pattern can be largely attributed to the much smaller value of K_3 in this solvent[2c] so that C is the principal form of the monosubstituted clusters. Formation rates of C were determined by monitoring spectral changes at 393 nm, the isosbestic point for eq 7 (L = $P(OCH_3)_3$). The slower second

$$Ru_3(CO)_{10}L(CO_2CH_3)^- + L \rightarrow Ru_3(CO)_{10}(L)_2 + OCH_3^- + CO \quad (7)$$

reaction (eq 7) was followed spectrophotometrically at 404 nm. Both reactions displayed a k_{obsd} vs. [L] rate profile consistent with eq 6. In this solvent k_1 was determined to be 5.8 ± 0.5 s^{-1} (25 °C) while the rate constant for the analogous step in the mechanism for eq 7 was found to be 1.1 ± 0.1 s^{-1} (25 °C).

The key observations here are the marked enhancements of the substitution lability of the trinuclear clusters upon forming the methoxycarbonyl adducts. For example, the half-life (0.087 s) of eq 2 (25 °C, P_{CO} = 1.0 atm, $[P(OCH_3)_3]$ = 0.0263 M, 10/90 THF/CH_3OH) is 3 orders of magnitude shorter than that (79 s) observed for the reaction of $Ru_3(CO)_{12}$ under analogous conditions. Investigations[8] of the latter reaction in hydrocarbon solvent have concluded that for $Ru_3(CO)_{12}$ substitutions two mechanisms are operative, a dissociative mechanism analogous to eq 3 and 4 and a second-order mechanism. The k_1 value for the former pathway is ~1×10^{-5} s^{-1} at 40 °C with $\Delta H^\ddagger$ = 32 kcal/mol[8] in contrast to the respective value of k_1 = 10.4 s^{-1} and $\Delta H^\ddagger$ = 12 kcal/mol noted here for $Ru_3(CO)_{11}(CO_2CH_3)^-$ in methanolic solvent.[9,10]

Previous workers have established that replacing CO by a stronger σ-donor/weaker π-acceptor ligand serves to labilize cis carbonyls in hexacoordinate mononuclear carbonyls.[11] This kinetic effect has been interpreted as resulting from stabilization of the transition state for CO dissociation, since, if anything, M–CO bonding in the ground state should be enhanced when one CO is replaced by such a ligand.[12] Similar mechanistic arguments have been proposed to explain the enhanced lability of CO from the clusters $Ir_4(CO)_{11}L$ and $Ru_3(CO)_{11}L$ (L = PPh_3),[10] but for these cases, the kinetic effects are smaller than found for the methoxycarbonyl adduct. A closer analogy would be rate enhancements seen for CO substitution of the carbene complexes $(CO)_5M{=}C(OR)R'$ (M = Cr, Mo, and W)[13] given that one

$$M{=}C(OR)O^-$$

cannonic form for the methoxycarbonyl is carbeniod. The more negative methoxycarbonyl ligand should be a better σ- and π-donor than the analogous carbene, thus even more strongly labilizing. The potential role of nucleophile adducts to CO in labilizing mononuclear carbonyl complexes has been discussed previously.[14] However, although the above comparisons may suggest that CO labilization occurs at the metal coordinated to the methoxycarbonyl, it should be emphasized that the labilization site is as yet unknown.

From these observations, it is clear that the role of the methoxide (or other strong nucleophiles) as a cofactor is reactions catalyzed by metal carbonyls may not only be to activate coordinated CO for further reactions but may also serve to labilize ligands to provide an open (or labile) coordination site on the same or adjacent metal center. This may prove especially important for catalysis of reactants such as dihydrogen that require coordination for activation.[15] In this context, it is notable that THF solutions of A react readily at room temperature with H_2 to give $HRu_3(CO)_{11}^-$ plus HCO_2CH_3 (identified spectrally).[16] In contrast, $Ru_3(CO)_{12}$ does not react measurably with H_2 under comparable conditions.

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(5) Earlier studies in this laboratory[2c] have demonstrated that $Ru_3(CO)_{11}P(OCH_3)_3$ in methanol solutions does not form detectable concentrations of the methoxycarbonyl adduct up to $NaOCH_3$ concentrations as high as 0.023 M.

(6) In a related study we have noted that the reaction of $Ru_3(CO)_{10}(\eta^2\text{-}CO_2CH_3)^-$, where the methoxycarbonyl group apparently bridges a Ru–Ru bond, reacts over a period of minutes with $P(OCH_3)_3$ to give $Ru_3(CO)_{10}(P(OCH_3)_3)(\eta^1\text{-}CO_2CH_3)^-$. Thus, it appears that C is not the $Ru_3(CO)_{10}(\eta^2\text{-}CO_2CH_3)^-$ species and furthermore that, under the reaction conditions, C is much more reactive with CO or $P(OCH_3)_3$ than to internal cyclization to give the bridged species.

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(9) Another unusual feature of the substitution reactions of A is the negative ΔS value (−13(cal/mol)/deg). In comparison positive ΔS values were noted for other cluster substitution reactions proposed to proceed via a dissociative mechanism (e.g., ref 10). We have no ready explanation for these differences except to note that the present case involves an anionic cluster in a protic solvent while the other documented examples were of neutral clusters in nonpolar solvents. One speculative explanation might be that charge redistribution and structural changes in the cluster accompanying eq 3 lead to restriction of solvent degrees of freedom. This question is the subject of further examination.

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